IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SEPRACOR, INC., Plaintiff, Counterclaim-Defendant v. DEY, L.P. and DEY, INC., Defendants, Counterclaim-Plaintiffs.	)	Civil Action No. 06-113-KAJ
SEPRACOR, INC., Plaintiff, Counterclaim-Defendant v. DEY, L.P. and DEY, INC., Defendants, Counterclaim-Plaintiffs.	)	Civil Action No. 06-604 KAJ

DEY'S REPLY IN SUPPORT OF ITS MOTION TO CONSOLIDATE

I. INTRODUCTION

Sepracor's response to Dey's motion to consolidate is simply another attempt by Sepracor to derail the schedule ordered by this Court. Sepracor essentially argues that if the two levalbuterol hydrochloride patent infringement actions it brought against Dey, Civil Action No. 06-113-KAJ (identified by Sepracor as Dey I) and Civil Action No. 06-604-KAJ (identified by Sepracor as Dey II) were consolidated, and the consolidated case used the Dey I scheduling order, Sepracor would be precluded "from having a fair and reasonable opportunity to discover

and prepare the issues on which it has the burden of proof in the Dey II case." *See* Sepracor Answering Br. (D.I. 70) at 1. Sepracor never identifies how the products that are the subject of Dey's two Abbreviated New Drug Applications ("ANDAs") differ or why Sepracor's infringement cases would differ. Instead, it simply argues that Dey's filing of a second ANDA is some sort of an "October surprise" intended to prejudice Sepracor. As detailed below, consolidation of the two cases and adoption of the Dey I scheduling order will not prejudice Sepracor.

First, Sepracor already has received sufficient information about both of Dey's ANDA filings to ascertain an infringement position. Sepracor's speculation that the products that are the subject of the two actions must be materially different because Dey filed two ANDAs, is therefore, disingenuous and misleading.

Second, Sepracor improperly accuses Dey of gamesmanship. Sepracor essentially argues that Dey delayed filing the second ANDA to prejudice Sepracor. "[T]he ANDA applicant has control over the timing as to when the patentee files…." Sepracor Answering Br. (D.I. 70) at 2. There is no support for Sepracor's allegation. Sepracor does not explain why it believes Dey would delay filing an ANDA and thereby risk the 180 days of product exclusivity given to the first to file pursuant to 35 U.S.C. § 355(j)(5)(B)(iv). This is because delay in filing its ANDA does not benefit Dey. In contrast, however, Sepracor benefits by a delay[1] in resolving Dey I and Dey II because each day of delay means another day that Sepracor can maintain its monopoly on the sale of levalbuterol.

[1] Sepracor's attempts to delay resolution of this matter have been evident since it asked this Court to adopt the extended scheduling order in "*Sepracor v. Breath Ltd.*, No. 06-10043-DPW (D. Mass.) (the "Breath action"), which this Court declined to do. At a recent hearing, the Massachusetts Court expressed concern about the length of the schedule. The court stated: "Now am I still right that it's not a typographical error to say 2008 for Markman?" *See* Transcript of Motion Hearing held on 10/17/06 in the Breath action at p. 10 ll 4-5 (attached as Exhibit A). At a later point the court stated "I am concerned about, you know, making the case move along. And I don't think I have anything [else] scheduled for 2008." *Id*. at p. 12, ll 11-13.

Sepracor's opposition to Dey's motion to consolidate Dey I and Dey II using the Dey I scheduling order is consistent with its pattern of trying to delay resolution of this matter and contrary to the statutory mandate that the parties expedite Hatch-Waxman cases. Applying the Dey I schedule will give Sepracor 17 months from the filing of the action to prepare its case—a generous amount of time under this Court's Local Rules. Moreover, although discovery has been ongoing since July 17, 2006, fact discovery is still in the early stages. For example, Sepracor has not yet provided complete interrogatory responses on its claim construction or infringement positions.

Sepracor has no basis to support its claim that consolidation of the cases using the schedule in place for Dey I will prejudice it. In contrast, delay in the resolution of the cases is prejudicial to Dey and to the general public as it may result in the delay of generic levalbuterol going to market.

II. ARGUMENT

A. SEPRACOR WILL NOT BE PREJUDICED IF THE CONSOLIDATED CASE HAS THE DEY I SCHEDULE

1. Sepracor's Theories of Infringement Will Be Similar if Not Identical in Dey I and Dey II

In its carefully written response, Sepracor never states that its theories of infringement in Dey I will differ from its theories of infringement in Dey II. Rather, it makes statements such as: "as to the issues on which Sepracor has the burden (*e.g.*, infringement of the patents-in-suit), the Dey I and II actions involve different ANDAs and different products"[2] and "consolidation of the Dey I and Dey II actions would expand Sepracor's proofs on issues of infringement." While it is

[2] Sepracor never defines "different products." It never states that there is any difference between the ANDA products at issue in Dey I and those at issue in Dey II that impact its infringement position. The Dey ANDA products do differ in the concentration of the active ingredient. The concentration of the product itself is not claimed in any of the patents and, therefore cannot have any bearing on infringement.

not clear what Sepracor means by "expand Sepracor's proofs," it is clear what Sepracor never states. Sepracor never states that consolidation would expand or change its theories of infringement. That is because it will not.

The formulation of Dey's ANDA products are not a mystery to Sepracor. Under the provisions of the Hatch-Waxman Act, an ANDA filer (here Dey) must offer the patentee (here Sepracor) access to portions of the ANDA so that the patentee can determine whether or not to bring an infringement action. 21 U.S.C. § 355(j)(5)(C)(i)(III). Sepracor requested and received portions of Dey's ANDA and samples of its ANDA products under this provision. Sepracor knows that any theories of infringement it may have for the products that are the subject of Dey I are going to be the same as its theories of infringement for the product that is the subject of Dey II. Consolidation and adoption of the Dey I scheduling order will not prejudice Sepracor.

2. Applying the Dey I Schedule to the Consolidated Action Will Give Sepracor 17 Months From the Filing of Dey II Until Trial

Sepracor will not be prejudiced if the cases are consolidated and have the Dey I schedule because Sepracor will still have 17 months from when its complaint in Dey II was filed until trial. Delaware Local Rule 16.2 provides that "trial shall be scheduled to occur within 12 months, if practicable, and no later than 18 months, after the filing of the complaint, unless the Court certifies that, because of the complexity of the complaint" a longer period is required. Del. LR 16.2. Sepracor filed its complaint in Dey II on September 27, 2006. Under the scheduling order in Dey I, trial will not take place until February 25, 2008.[3] Thus, applying the Dey I schedule to the consolidated case will result in a period of 17 months from the filing of the complaint in Dey II until trial.

[3] In Dey I, Dey requested a trial date of 18 months from filing of the complaint. Sepracor had asked for a trial date 30 months after filing of the complaint. The Court entered a scheduling order providing for a trial date 24 months after filing of the complaint.

Given that the issues of law and fact are the same in the Dey I and Dey II actions, and that Sepracor already has the benefit of discovery from the Dey I action, a scheduling order in the Dey II action that gives Sepracor a trial date 17 months from filing its complaint is more than adequate for Sepracor to have a "fair and reasonable opportunity to discovery and prepare the issues on which it has the burden of proof in the Dey II case."

B. DEY WOULD BE PREJUDICED IF THE SCHEDULE FOR DEY I IS EXTENDED

According to Sepracor "Dey will not be prejudiced by enlargement of the calendar in the Dey I matter since, in any event, Dey can not obtain FDA approval … until after the resolution of the Breath action in Massachusetts." Sepracor Answering Br. (D.I. 70) at 7. This argument does not comport with the law. The Hatch-Waxman Act sets out the events which can trigger the 180-day exclusivity of the first ANDA filer. Several of those triggering events do not require the entry of a final unappealable court decision in the litigation involving the first-to-file applicant. *See* 21 U.S.C.§ 355(j)(5)(D). Resolution of the Breath action is not, therefore, a necessary prerequisite to Dey obtaining FDA approval to market its product.

Sepracor argues that Dey's position that Dey I and Dey II should be consolidated is somehow inconsistent with its position that Dey I should not be consolidated with the case Sepracor brought against Breath. There is no inconsistency. First, the parties are the same in Dey I and Dey II whereas the defendants in Dey I and in the Breath action are not. Second, the patents asserted in Dey I and Dey II are different than the patents asserted in the Breath action. In Dey I and Dey II, five method-of-use patents are asserted against Dey. All five patents are related and have the same specification. Indeed, the claims of the patents-in-suit are so similar that the examiner determined that the claims of the different patents are simply obvious

variations of each other and required the applicants to file terminal disclaimers.[4] In the Breath action six patents are asserted. In addition to the five patents asserted against Dey, Sepracor asserted a sixth and unrelated formulation patent—U.S. Patent No. 6,451,289 (the '289 patent)—against Breath. (A copy of the '289 patent is attached as Exhibit B.) Sepracor has not asserted the '289 patent against Dey, presumably because it has determined that it has no Rule 11 basis for doing so. This further highlights that there are differences between the products at issue in the Breath action and the products at issue in Dey I and Dey II. The differences between the Dey products and the Breath products provide yet another reason why Dey opposed consolidation of Dey I with the Breath action.

In contrast to the Breath and Dey I litigations, Dey I and Dey II meet the requirements for consolidation—the issues of law and fact are the same. This is not true of Dey I and the Breath action which involve different parties, different products and different patents. As Sepracor's counsel stated to the Massachusetts Court in the Breath action:

> Ms. Dadio: Our proofs obviously will be different in the two [Breath and Dey] cases ----
>
> The Court: yes.
>
> Ms. Dadio: because it's two different companies. However, the defenses – the allegations of validity and non-infringement – depend upon the particular product that are different generics…

[4] A terminal disclaimer is used to dedicate a portion of the patent term to the public. The United States Patent and Trademark Office may order the entry of a terminal disclaimer to overcome obviousness-type double patenting rejections. The entry of a terminal disclaimer prevents an application for an obvious variation of an existing patent from being used to extend the patent term of that existing patent by disclaiming any part of the patent term granted for the patent issuing from the application which extends beyond the term of the existing patent. *See* 35 U.S.C. § 253 and 37 C.F.R. § 1.321.

C. CONSOLIDATING DEY I AND DEY II WITH THE SCHEDULE OF DEY I IS IN KEEPING WITH THE STATUTORY REQUIREMENT THAT THE PARTIES EXPEDITE THE ACTION

The Hatch-Waxman Act provides that the parties shall "reasonably cooperate in expediting the action…" 21 U.S.C. §355 (j)(5)(B)(iii). Consolidation of Dey I and Dey II with the Dey I schedule is reasonable, will not prejudice either party, will increase judicial economy and will expedite the case as required by the statute. Accordingly, Dey respectfully requests Dey I and Dey II be consolidated for all purposes, and that the consolidated case remain on the Court ordered schedule in place in Dey I.

III. CONCLUSION

For the foregoing reasons, Dey respectfully requests this Court to Order Civil Action No. 06-604-KAJ be consolidated with Civil Action No. 06-113-KAJ and that the scheduling order already in place in Civil Action No. 06-113-KAJ be ordered for the consolidated case.

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Dated: November 15, 2006
175209.1

CERTIFICATE OF SERVICE

I hereby certify that on the 15th day of November, 2006, the attached **DEY'S REPLY IN SUPPORT OF ITS MOTION TO CONSOLIDATE** was served upon the below-named counsel of record at the address and in the manner indicated:

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_____
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EXHIBIT A

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

* * * * * * * * * * * * * * * * * * *

SEPRACOR, INC.
Plaintiff

VERSUS CA-06-10043-DPW

BREATH LIMITED
Defendant

* * * * * * * * * * * * * * * * * * *

BEFORE THE HONORABLE DOUGLAS P. WOODLOCK

UNITED STATES DISTRICT COURT JUDGE

MOTION HEARING

OCTOBER 5, 2006

APPEARANCES:

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Courtroom No. 1 - 3rd Floor
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Boston, Massachusetts 02210
10:30 A.M. - 11:25 A.M.

Pamela R. Owens - Official Court Reporter
John Joseph Moakley District Courthouse
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THE COURT: Well, I brought you in principally because I looked at this and thought I had this kind of sinking feeling that this was going to be a high maintenance case because the parties seemed interested in exploring the full

dimensions of Rule 9B and 12E. And I guess my hope is that you will disabuse me of the prospect of this being a high maintenance case or, in the alternative, I will disabuse you of that. And perhaps a way of doing this is just to ask as a practical matter what difference does it make. I mean, I understand Judges have written things saying you can't satisfy 9B by discovery at a later point. On the other hand, is there something about this case that suggests that an inordinate amount of time should be spent parsing the pleadings to get to the bottom of what precisely it is that the inequitable conduct claims consist of?

MS. DADIO: Your Honor, if I might, Susan Dadio for Sepracor.

THE COURT: Right.

MS. DADIO: Sepracor brought this motion, Your Honor, with the best of intent. I believe that the motion, in fact, shows the very judicious selection which Sepracor made.

THE COURT: I'm not suggesting bad faith. I am suggesting that most of us have only 24 hours in the day to perform various kinds of activities. And unless there is an absolute need for a certain kind of motion practice, I think

it's best left undone.

MS. DADIO: I understand.

THE COURT: So what's the need for this?

MS. DADIO: The need here is two-fold, Your Honor. The need is first with respect to the many obligations of inequitable conduct concerning patentability, our series of six statements, very general at that, that anyone -- they define Sepracor as the inventors, anyone in the company, any of their attorneys. So if we look at this motion, it's not purely

requesting a page and line citation to the particulars of the file record. Obviously, that is something that should be required. But the real process --

THE COURT: Should be required --

MS. DADIO: It should be.

THE COURT: -- in the complaint?

MS. DADIO: Yes, Your Honor.

The crux of or the crucial part here is the factual basis for alleging each of the patentability representations are false and, moreover, who at Sepracor knew that such representations were false. Those are very important items that, even given sort of the volume of paragraphs, shall we say, of Breath's complaint, still cannot be deciphered from the pleadings. And we're all aware that inequitable conduct must be pled with the level of particularity. And standing here today, there could be any number of possibilities of

inequitable conduct that I could fathom that Breath might be contemplating with respect.

THE COURT: So, why didn't you file an interrogatory?

MS. DADIO: Because, Your Honor, there are so many here and we do have a limited number of interrogatories. In essence, that would be punishing Sepracor. Sepracor would have to be curing --

THE COURT: You'll be the first lawyers in America who haven't asked for relief from limitations of the number of interrogatories in a complex case. This is a case in which I looked at my calendar and thought I had made a typographical error because the Markman hearing is in 2008.

MS. DADIO: That's correct, Your Honor.

THE COURT: I suspect that the parties will work out numbers of interrogatories and that sort of thing. I mean, you know, it's one thing to feel constrained. It's another thing to use the customary constraints for the ordinary case as a basis for asking for something more at the outset.

MS. DADIO: Your Honor, I don't think Sepracor is asking --

THE COURT: What do you want, a 700-page complaint; is that what you want?

MS. DADIO: No, Your Honor. We would just like what is required by the law, for them to claim their particular

allegations of inequitable conduct with the requisite level of particularity. If Breath chooses to allege umpteen million allegations, then the volume of it is and must be what it is. But again, there are very strong public policy issues that the Federal Circuit has articulated with respect to claiming inequitable conduct with particularity.

THE COURT: What are you doing in your discovery now?

MS. DADIO: I'm sorry, Your Honor?

THE COURT: What's going on in discovery now?

MS. DADIO: We are in document production mode essentially at this point. Interrogatories have been exchanged and document requests and document production.

THE COURT: Do the interrogatories touch on inequitable conduct?

MS. DADIO: Yes, they do, Your Honor.

THE COURT: What do they ask for?

MS. DADIO: Without having them specifically, again they do ask for a certain level of contentions with respect

to -- I would be stating out of turn here if I stated specifically. I know at least they cover those claims that we did not set forth in this complaint. As to whether or not they did address these, I would have to --

THE COURT: I'm sorry. I'm misunderstanding. I don't fully understand. You have contention interrogatories

that address so much of the --

MS. DADIO: Inequitable conduct.

THE COURT: -- inequitable conduct that you think are adequately pled in the complaint?

MS. DADIO: I believe that's correct, Your Honor. And I'm not a hundred percent accurate as to whether or not those interrogatories include the full scope or not, so I would be speaking out of turn by answering that question.

THE COURT: Okay.

MS. DADIO: I believe Ms. Mazzochi might know the answer to that because I believe they were due yesterday.

MS. MAZZOCHI: Your Honor, if I may, I think their interrogatory number (7) specifically asked for Breath to identify the factual bases for all of the allegations set forth in this particular count relating to unenforceability. And we are, in fact, planning on complying with that and providing a detailed response, you know, to the extent that we can.

THE COURT: Is the detailed response as complete as is apparently asked for in the motion for a more definite statement?

MS. MAZZOCHI: Your Honor, I believe that our answer as it presently stands does, in fact, include some additional citations to particular things within the prosecution history.

THE COURT: Some, but why not all?

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MS. MAZZOCHI: We can certainly do all of them, Your Honor. I mean, the prosecution history contains a number of declarations and statements in there.

THE COURT: Well, that may be true. But this is for you as well. Ultimately, I'm going to have to decide this. Ultimately, I'm going to have to be pointed in the direction of those statements that you say are misrepresentations. And that's perhaps a tedious process, but one that better be done here. Now, what was the reason for not including it in the counterclaim?

MS. MAZZOCHI: Well, Your Honor, I think that the point with the counterclaim was to identify the particular topics that we felt had not been properly presented to the Patent and Trademark Office and we did enumerate those in the counterclaim. For example, the statements relating to the allegation of reduced side effects in association with the R-isomer that was claimed, that's specifically identified. The fact that the written description -- the representations that Sepracor made to the Patent and Trademark Office that the written description of their specification adequately disclosed the R-isomer, that is also identified in our counterlcaim.

THE COURT: Identified as a general proposition. In what way didn't it?

MS. MAZZOCHI: In what way does it? Well, the allegation is that the written description does not support

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their statement.

THE COURT: In what particular?

MS. MAZZOCHI: Well, because the specification doesn't say anything about how these reduced side effects have been conceived of as the inventive aspect of the invention by the inventor.

THE COURT: And is that what your allegation said with specificity?

MS. MAZZOCHI: We believe that it does, that the written --

THE COURT: So you think you said who, what, where and when --

MS. MAZZOCHI: Right.

THE COURT: -- with specificity in your complaint or counterclaim?

MS. MAZZOCHI: Right. The who are the individuals who were making the arguments to the Patent and Trademark Office --

THE COURT: Are they identified?

MS. MAZZOCHI: -- i.e., the patent attorneys.

THE COURT: Patent attorneys generally are identified.

MS. MAZZOCHI: Well, I think there was only one or two individuals.

THE COURT: And is the document in which this is

made identified?

MS. MAZZOCHI: Within the prosecution history?

THE COURT: No, within the complaint or counterclaim.

MS. MAZZOCHI: Well, the complaint identifies the prosecution history. The actual --

THE COURT: How big is the prosecution history?

MS. MAZZOCHI: When you --

THE COURT: It's somewhat bigger than a bread box, I would suspect?

MS. MAZZOCHI: Actually not my bread box. No. The bulk of the prosecution history is taken up with the -- you know, what I would consider to be some of the procedural things, you know, the records of the filing fees.

THE COURT: Look, this is for both of you. I have no burning desire to make my mark on proliferating the meaning of Rule 9B or 12E. But if pressed, of course, I'm really interested in making sure the cases move along promptly, efficiently, and the parties get to the core of what they are entitled to. 9B practice is not -- to my mind, anyway -- particularly productive ordinarily. It just suggests that the parties are stuck in the mud at the start.

I think my view is that the complaints in the ballpark -- counterclaims in the ballpark may be there with a hockey stick in terms of particularity and this can be handled

by the interrogatories. But those interrogatories better be very specific because if you don't have it in the interrogatories, you don't have it. And I'm not going to let, you know, a re-reading of the prosecution history come percolating up at a later point in this case --

MS. MAZZOCHI: Understood, Your Honor.

THE COURT: -- as grounds for a very difficult to prove claim, difficult to prove because the state of the proof is high.

But that then raises the larger issue. Why have the pleasure of encountering these kind of disputes throughout this very lengthy time period before we even get to Markman?

MS. MAZZOCHI: I hope that, Your Honor. And to that end, we have already produced all of our documents. We've reproduced the full ANDA to Sepracor, R&D documents, prior art documents, file history documents. So, we've produced, as far as I'm aware, all of the information that they have asked for.

THE COURT: That sounds good to me. But you shouldn't want to be bringing back disputes on discovery here unless they are absolutely necessary. You have got lots and lots of time, more time than I would let anti-trust cases go, to develop this case. I suggest you use the time well. And it would not be used well in preliminary posturing and tips which is not to say that there isn't a good faith basis for bringing the motion or that the counterclaim is beyond the pale. But I

just want to get on with it.

Now I'm told that the interrogatory answer was due yesterday, but it's going to appear manyana.

MS. MAZZOCHI: Monday. They will have it done on Monday.

THE COURT: I mispronounced it. Monday.

MS. MAZZOCHI: Yes.

THE COURT: But it better be specific about this.

MS. MAZZOCHI: It will be, Your Honor.

THE COURT: And that's the way I'm going to deal with it. You're apparently going to get what you want in this. I certainly hope you do.

MS. MAZZOCHI: I do, too, sir.

THE COURT: And I think if you don't, then you just ask them for some more. But that's how we're going to deal with this aspect of the matter.

So I'm denying the motion for a more definite

statement with recognition that refinements can be provided in the interrogatory answers to be filed relatively soon and that you'll move on to address the merits rather than be concerned with trying to bring discovery or such related pleading issues to me. I'm going to deal with it on a practical basis as best I can here, which is you're entitled to anything that bears on the case. We'll tidy up the pleadings when it becomes necessary, although I think you've got notice of some

suggestion of problems for inequitable conduct, notice of what they think are some potential for problems, and we'll go from there.

Now, am I still right that it's not a typographical error to say 2008 for Markman?

MS. DADIO: That's correct, Your Honor. It's not a typographical error.

THE COURT: So what's going to happen before then, an incredible amount of discovery?

MS. MAZZOCHI: Your Honor, Sepracor, for example, has identified 24 individuals in their initial disclosures. So it's our hope that within the next 30 days we're going to get those depositions underway. And with the holidays, that is going to keep us more than busy.

THE COURT: Well, that just gets you into 2007. What gets you into 2008?

MS. MAZZOCHI: Well, then we've got the expert phase and we expect, based on my personal experience with cases similar to this one, that there are going to be multiple experts addressing a variety of issues. And that is going to be the heart of the case.

THE COURT: Okay. Now, should I be staying awake

late at night throughout the year 2007 worrying about the number of claims that need to be construed here or are the parties going to work diligently to narrow that to only those

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that are truly in dispute?

MS. MAZZOCHI: It's my anticipation, based on reading some of their initial positions in this case, that there is likely to be three terms that are going to require construction by the Court. I'm going to obviously try to work with plaintiff to see if we can get pinpointed exactly where the difference is between where the parties lie on that so that we can try that.

THE COURT: And is this all going to happen before the Markman hearing or is it going to happen before summary judgment or in connection with summary judgment? Do you know?

MS. MAZZOCHI: It depends.

MS. DADIO: Excuse me, Your Honor. When we negotiated the information that we provided to the Court, we had agreed that Markman would occur before summary judgment.

THE COURT: No, I understand that. But has anything happened that would suggest that maybe there could be conflated summary judgment?

MS. DADIO: Well, depending upon their interrogatories with inequitable conduct.

THE COURT: All right. Well, is it all inequitable conduct? That's going to be the issue. It's certainly not the issue for claim construction, is it?

MS. DADIO: No, Your Honor.

THE COURT: So inequitable conduct is something for

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summary judgment.

MS. DADIO: But without claim construction. Claim construction will be at least -- we believe, to the extent Breath believes there is a dispute with respect to the way the claims would be construed, that is necessary in order to have a determination of infringement and validity.

THE COURT: Well, I understand the way in which sometimes cases are developed or patent cases are developed. And, frankly, I think I probably said this at our scheduling conference. I don't think that I'm aware of the perfect time to do Markman hearings. I am concerned about, you know, making the case move along. And I don't think I have anything scheduled for 2008. Now, that may be something you should fear, but it just seems like a long time away before I have to deal with this in a substantive sort of way. I defer to counsel in patent cases on when to do the Markman hearing. But my overarching interest, as I've indicated, is to try to get this resolved as promptly as possible or at least straightened away as promptly as possible. But those are simply random thoughts that perhaps would be helpful in organizing your own thoughts about how the case proceeds further here. Is there anything else we need to talk about?

MS. DADIO: Deanne --

MS. MAZZOCHI: Go ahead.

MS. DADIO: There is a potential, Your Honor.

We're trying to work out the particularities of a protective order in this case. And we don't have complete confirmation from Breath as to whether or not we are possible, but there appears to be at least two issues with respect to the entry of a protective order that the parties seem to be at an impasse with respect to. And we would anticipate that a motion may be

necessary.

THE COURT: So, give me a sneak preview. What's the problem?

MS. DADIO: There are two main issues with respect to -- I think that at least are concrete. The first issue is that Breath specifically wants to put a restriction in the protective order that prohibits Sepracor from utilizing its information to go to the FDA -- in particular, USP. And there is a case from this district --

THE COURT: Wait a minute. I just want to crystallize this. You received information in discovery that you would like to use with the FDA?

MS. DADIO: Yes, Your Honor.

THE COURT: And you said something about USP.

MS. DADIO: That is the United States Pharmacopoeia. It is -- for lack of a better term, it's somewhat -- not an arm. It's not an agency, but it has some level of affiliation with respect to FDA. These particular cases, Your Honor, the statutory nature of the Hatch-Waxman,

Breath had to file an abbreviated new drug application in order to seek approval to go on the market with its generic copy of Sepracor's very successful XOPENEX product. And they have produced that ANDA to us. And obviously, if there are some issues for which the FDA should be aware about, Sepracor should have the ability to discuss that with the FDA. A case in this district, Aventis v. Cobalt, which counsel is very familiar with, dealt with an issue on a protective order where there was a claim that in the protective order that the information in this protective order -- confidential information -- could only be used for purposes of litigation. The innovator drug company

wanted to go to the FDA with certain information. And their argument, which would be the same as ours, is that that information is not confidential to the FDA because they are already aware of it. And therefore, Sepracor should be entitled to go to the FDA with any of that material.

THE COURT: What -- and open another front; is that what --

MS. DADIO: From a safety issue for --

THE COURT: Well, but I mean, it's opening another front. Am I to understand that the purpose of going to the FDA is not merely to raise a hue and cry as a generally interested citizen, but as a competitor who is concerned about FDA action adversely affecting you?

MS. DADIO: Well, it wouldn't be so much, Your

Honor, an action that would be adverse. It would be in the form of a citizen's petition and not even set up -- it's difficult for me to articulate what it would be because certainly we have no intention or no plans, I should say, at this time to be doing any of this type of activity. However, it's something that once we do take a look at their documents -- I think Ms. Mazzochi said some of them are being produced today -- should there become an issue, for instance, with respect to safety, there is certainly a public policy issue of that and there's also the issue of whether or not --

THE COURT: Just a moment. Let me just understand this. Let's assume you get the documents under the confidential agreement. You turn them over to the FDA. I can conceive of circumstances -- I'm not fully familiar with this dimension of Aventis. You turn them over to the FDA. Are they confidential in the hands of the FDA?

MS. DADIO: I'm sorry, Your Honor?
THE COURT: Are they confidential in the hands of the FDA once they are turned over to the FDA?
MS. DADIO: Well, they're not confidential, Your Honor, because the documents that would be handed over are already in the possession of the FDA. They would be, for instance, part of the ANDA which the FDA already has.
THE COURT: But aren't they confidential? Does the FDA have some sort of confidentiality provisions with respect

to this or are all these documents already in the public record now?
MS. DADIO: To my understanding, they are not in the public record until approval is obtained. So until --
THE COURT: But has approval been obtained?
MS. DADIO: Approval cannot be obtained, Your Honor, because this lawsuit -- by the institution of this lawsuit, there is an automatic 30-month stay for which Breath cannot receive approval for its product and did therefore not go on the market.
MS. MAZZOCHI: Your Honor, if I can answer that, essentially if Sepracor were to take Breath's confidential documents and file a citizen's petition with FDA, that citizen's petition would be part of the public record, including all the exhibits attached to it.
THE COURT: Even if the -- let me just understand. Let's assume that the universe of documents that they submit in connection with their citizen's petition consists solely of materials that you have already submitted to the FDA.
MS. MAZZOCHI: Right.
THE COURT: There's nothing else out. As I

understand it, right now, those are confidential documents in the hands of the FDA, remain confidential until the FDA grants your petition?

MS. MAZZOCHI: Right. And even some of those might

still be maintained as confidential, particularly if it relates to manufacturing methods and that sort of thing. There actually are provisions by which FDA can maintain some information as trade secrets. And this is actually common, including with the brand companies, is that when you file for FOIA requests with FDA, specific manufacturing information is often redacted out because it's maintained as a trade secret under the statute.

By contrast, if Sepracor were to file a citizen's petition with FDA, that is public. It will go up on the FDA website in their docketing department. There is no provision by which a citizen's petition that Sepracor submits to FDA can be maintained as confidential.

THE COURT: All right. Now, what's the status of other less well-placed citizens in obtaining information concerning a proceeding with the FDA like this? The FDA doesn't have an adversarial proceeding taken with respect to this?

MS. MAZZOCHI: Oh, no. I mean, once FDA issues -- once FDA issues --

THE COURT: What does FDA do? Does FDA just listen to you? Does Sepracor as the brand have some rights to get in there and discuss the matter with the FDA?

MS. MAZZOCHI: I mean, technically with a citizen's petition --

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THE COURT: Put to one side the citizen petition. Let's assume a citizen's petition is not filed.

MS. MAZZOCHI: Okay.

THE COURT: You file whatever it is that you file.

MS. MAZZOCHI: Right.

THE COURT: We're looking for some sort of speed-up to get generic out there. The brand is concerned about that. So, does the brand have any way of getting into -- involved in the FDA proceeding without a citizen's petition?

MS. MAZZOCHI: Officially, I believe the correct route is through the citizen's petition, you know, what they do unofficially through controlled correspondence or something like that. I don't know all the details.

THE COURT: But they are not -- they are not provided with an opportunity to comment on it officially, whatever it is that you submitted to the FDA.

MS. MAZZOCHI: Right. They don't get any preference above and beyond the general public in terms of what we submit to FDA.

THE COURT: And, so, what you've submitted to the FDA right now -- everything that you've submitted to the FDA is confidential?

MS. MAZZOCHI: Right. I believe the fact that we have submitted an ANDA to FDA is public information. But with regard to the actual contents of the application itself, that

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is maintained as confidential by FDA.

MS. DADIO: I would think --

MS. MAZZOCHI: And then it's my understanding that once our ANDA receives FDA approval --

THE COURT: But it can't during the pendency of this case or for 30 days --

MS. MAZZOCHI: For 30 months.

THE COURT: Thirty months?

MS. MAZZOCHI: Right.

THE COURT: Thirty months after the case is filed, it's can't until its disposition?

MS. MAZZOCHI: Right. It's not actually -- it's under Hatch-Waxman, it's 30 months from the day on which I believe the notice of paragraph (4) certification is received by Sepracor and that is what starts the clock ticking assuming that they have filed suit which obviously they did. So we're currently operating under a 30-month stay of final FDA approval. We can receive tentative FDA approval, but we can't receive the actual final FDA approval that permits us to go to market.

THE COURT: And what does tentative approval mean?

MS. MAZZOCHI: Tentative approval means that our drug has passed all safety and efficacy standards and the FDA would otherwise be able to approve the drug finally but for the pendency of this action. Essentially, we would -- to get our

final FDA approval, the 30 months needs to pass in this case or we need to secure a judgment in our favor on all of the patents either based on non-infringement, invalidity, or unenforceability. So, for example, if you were to find --

THE COURT: When was the -- you know, I'm doing this by horseback.

MS. MAZZOCHI: Right.

THE COURT: But the Section 4 certification which was --

MS. MAZZOCHI: I believe the paragraph (4) --

THE COURT: -- paragraph (4).

MS. MAZZOCHI: -- certification date was roughly November-December '05. I'd have to double-check the actual date.

THE COURT: And was it more or less coincident with the filing of the suit?

MS. MAZZOCHI: I'm sorry?

THE COURT: Was it more or less coincident with the filing of the suit?

MS. MAZZOCHI: Yes. They have got 45 -- after we serve them with the notice of our paragraph (4) certification, they have got 45 days to file the lawsuit. And if they do, then that means we're going to be stayed for 30 months. And they did. I believe they did, in fact, file within the 45 days, so that triggered the 30-month stay provisions under

Hatch-Waxman.

THE COURT: Now, why would the FDA, in the face of the lawsuit, go forward with tentative approval?

MS. MAZZOCHI: It's been --

THE COURT: Is it just an efficacy determination or is it --

MS. MAZZOCHI: Yes. The distinction between an NDA and an ANDA is that with an abbreviated new drug application, you are demonstrating that your generic drug is bio-equivalent to the reference-listed drug; i.e., the brand drug. So there's -- you know, you don't have to do the same types of toxicology studies or phase one, phase two, phase three clinical studies. So what we've done here is we've done the clinical investigations required to be considered to be bio-equivalent;

i.e., we should -- you know, if someone takes the brand version, if they take the generic version, they should experience the same therapeutic effects. I mean, there's some --

THE COURT: But that's the concern of the FDA. The FDA is indifferent on the question of patent, I mean, in the sense it's not going to assert itself in any way on the question of patent.

MS. MASSOCHI: No, no. I mean, it's been our experience that typically when FDA knows that an ADNA is the subject of litigation, they tend to move a bit slower. But

typically, it's around -- depending on the complexity of the drug and the nature of the therapeutic issues and the chemistry and how responsive you are to FDA, it generally takes anywhere between 18 to 36 months to get your tentative approval from FDA. And then once they issue tentative approval, that would be the point in time where we would be able to say, you know, okay, what's our litigation status. I mean, as of right now, you know, if this case were decided favorably on Cobalt tomorrow, we couldn't go to market because we don't have tentative approval from FDA. Once we get tentative approval from FDA, you know, assuming that that does happen in the future, then it will become a question what's the status of this litigation in terms or our being able to enter the market.

THE COURT: All right. Now, in terms of protective order, is there any meaningful way to restrain the use of the confidential information by the FDA -- that is, restrain the FDA from making disclosure of it on their website?

MS. MAZZOCHI: As of right now, FDA cannot

disclose.

THE COURT: No. Let's assume that a citizen's proceeding or whatever it's called --

MS. MAZZOCHI: Right.

THE COURT: -- is initiated. FDA would have to be a party to this proceeding to constrain their disclosure of it.

MS. MAZZOCHI: Right.

THE COURT: And the only way to constrain disclosure would be on the parties here for their use in the litigation. Is that -- do I fairly state that?

MS. MAZZOCHI: Right. I mean, we would have no ability to go to FDA and say "please place the documents they attach to their citizen's petition under seal." I mean, you know, FDA wouldn't -- they wouldn't care.

THE COURT: Well, they may not. The question is can they be made a party to this case for that purpose.

MS. MAZZOCHI: I don't know if that's ever been attempted. And it's because --

THE COURT: They have a supervening statute that directs what they're supposed to do?

MS. MAZZOCHI: Yes. I mean, you know, I'm assuming that FDA is going to say that here's our regulations when we get a citizen's petition in. Here's what we do and we present. It's part of the public record. So, I don't necessarily see that. I mean --

THE COURT: Apart from the desire of all parties to avoid disclosure of documents, what's it to you?

MS. MAZZOCHI: The reason why it's important to us, separate and apart from maintaining confidentiality of documents -- because obviously we're not the only generic

company out there. I mean, Sepracor is litigating against

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another generic company on this very drug. But it's been my experience with other brand companies -- and, again, I'm not saying this to try to impune Sepracor in any way -- that with FDA and with the USP -- because the USP does, in fact, act as a standard-setting organization -- there have been in the past in my own personal experience instances where the brand company, once they know that tentative approval is coming down the line, they try to run the FDA to file a citizen's petition making allegations of safety and efficacy concerns. And what that will wind up doing is if FDA --

THE COURT: Isn't that going to happen sooner or later?

MS. MAZZOCHI: Yes. To me, I don't necessarily think that --

THE COURT: They have a -- you know, they have a competitive interest in not having you on the market, you and everybody else on the market, all the other generics on the market.

MS. MAZZOCHI: Right.

THE COURT: That exists no matter what stage this litigation is in. It becomes more salient when there's a temporary approval in the pipeline, but they always have the interest in filing a citizen's petition. And then it's really a question, I guess, of timing when they do it. But I still don't understand exactly what you gain or what you lose from

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the disclosure of whatever it is that you've submitted to the FDA. Now, I can see if it's that you're disclosing your chemical formulations to other generics who can do what you've

done -- you know, a kind of knockoff of whatever it is that they have got -- but I don't understand what else would be of value to you.

MS. MAZZOCHI: Right. Well, for example, with the United States Pharmacopoeia, the USP, one strategy that we've seen is what the brand company will try to do is set up what's -- the USP is a standard-setting organization.

THE COURT: I'm sorry?

MS. MAZZOCHI: The USP is a standard-setting --

THE COURT: Is a standard setting -- okay.

MS. MAZZOCHI: -- organization.

THE COURT: Right.

MS. MAZZOCHI: And what they do is they will set standards for your drug has to comply with X, Y and Z in order to be certified as USP. For all practical purposes, if there's a monograph in the United States Pharmacopoeia that says here's certain standards that your drug has to meet, if it doesn't meet them, you will not have a market, your drug will not be --

THE COURT: Irrespective of whether the FDA approves --

MS. MAZZOCHI: Irrespective of whether FDA approves it. It just doesn't happen. So, what brands have attempted to

do in the past is because they are the ones who effectively craft the monograph is they will try to put things in the monograph where you can't make a drug unless you're infringing their patent.

THE COURT: Okay. But I still don't understand what the timing issue is on that. Sooner or later, they want to do that, I guess.

MS. MAZZOCHI: Right.

THE COURT: It makes sense that that's what they want to do.

MS. MAZZOCHI: Sure. And, Your Honor, if that's what they want to do, to me they shouldn't be able to use our confidential information that they get.

THE COURT: But isn't your confidential information sooner or later going to get out? Isn't it --

MS. MAZZOCHI: No, not necessarily. That's what I'm saying is that FDA, even for parts of our application that want to be made public subsequent to FDA approval, they will maintain as confidential certain trade secret information such as relating to certain manufacturing specifics and that sort of thing.

THE COURT: Okay. Well, but doesn't that bring me back around to the dimensions of the protective order, a protective order dealing with traditional trade secret information. Manufacturing information, for example, could be

covered, couldn't it, and others not, other stuff that would otherwise be disclosed in any event.

MS. MAZZOCHI: Right. Well, I mean, we're not looking to designate as confidential under the protective order things that -- you know, information that we don't consider to be private.

THE COURT: Well, let me just suggest a standard which is to say that those materials which would otherwise be maintained confidential by the FDA would be maintained confidential under a protective order if submitted to the FDA.

MS. MAZZOCHI: I follow you.

THE COURT: And that would permit, I guess -- I don't know enough about citizen's petitions or whether this

would be inadequate for a citizen's petition, but that would permit them to file their citizen's petition if they think that that's appropriate.

MS. MAZZOCHI: Right.

THE COURT: I mean, I'm just trying to think through. This is all tentative. As you know, this is the first I've heard of it. I'm just trying to think through so that perhaps I'll feel or shape the way in which you approach it. One way of looking at this -- I mean, certainly you don't want to use discovery. Discovery ought not to be available for purposes of litigating some other crime. As it appears now, there is an incentive to file one of these lawsuits because it

gives you another 30 months by doing so while some poor federal judge is bedeviled with claim construction taking place perhaps not even in his own lifetime.

MS. DADIO: If I might say something in that regard, Your Honor, the idea of filing the lawsuit with patents that are still listed in the orange book for particular innovator company -- we prefer to use the innovator as opposed to brand -- company, they still have to deal with the patent issues. So, it's an incentive for the generic to deal with the patents up front as opposed to ramping up, going on to market, and then be the innovator company coming in and suing them for patent infringement.

THE COURT: I think I understand what the various compromises are in the Hatch-Waxman Act. But I'm really trying to understand the fair evaluation of the availability of information that I would otherwise not permit.

MS. DADIO: That's correct, Your Honor. And we have attempted and with your guidance maybe we could go back

with them. Because we had attempted to fall in line with the Aventis case. If I'm correct, that's cited at 355 F.Supp.2d 586. That's from the District of Massachusetts. That particular case, we have tried to propose language such that it would fall within the gamut of that. Maybe we will try again.

THE COURT: Well, I'll have to look at it, I'm

sure, at some point. But that's one aspect. What's the other? You said there were two things that were causing problems in the protective order. What's the other one?

MS. MAZZOCHI: The only other thing, Your Honor, is we just wanted to have a two-tiered system for particular information. I mean, the bulk of it really has got to be designated as confidential and they have got in-house people who are going to be able to access it. But with respect to a couple of particulars for the manufacturing process -- and in particular, for our formulation for how we actually make these nebular capsules that go in the inhalers and any specifics with regard to a potential future commercial launch date, we wanted the opportunity to be able to designate that type of extremely sensitive commercial information as outside counsel. And we spoke with Ms. Dadio and said, look, if it gets to a situation where you feel the need to discuss this with your in-house counsel, we're perfectly happy to work with you so that you can get them whatever information they need to know. But, you know, we would prefer to have that second tier in the protective order just so that we don't have to keep coming back before Your Honor to say, can we please have leave from this aspect of the protective order so that their in-house people don't gain access to it. So, that's -- I mean, that's

basically the issue on the protective order.

THE COURT: What is the problem with that?

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MS. DADIO: There's two primary issues, Your Honor. The first, as Ms. Mazzochi had referred to, there is another parallel paragraph (4) case on this product which Sepracor --

THE COURT: Where is that?

MS. DADIO: That is in the District of Delaware against a generic company called Dey, D-e-y.

THE COURT: And where is that in terms of its travel at this point?

MS. DADIO: Technically, it was filed after, but there are certain aspects of that that are further along. For instance, there is a protective order already agreed to and in place signed off by the Judge in this case. And that is the protective order that we were trying to --

THE COURT: And just so I understand, that case was filed more or less at the same time as this one or not?

MS. DADIO: It was filed shortly after this particular case.

THE COURT: And is Markman taking place in that case in 2008?

MS. DADIO: I don't believe that's correct, Your Honor.

THE COURT: All right. Why is it not correct?

MS. DADIO: It is not occurring in 2008 if memory serves me correctly.

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THE COURT: Why?

MS. DADIO: Because the Judge in that particular case set a different schedule with respect to this particular matter.

THE COURT: So I'm as soft as a grape as opposed to the Judge in Delaware on this?

MS. DADIO: No, Your Honor. With all due respect, certainly the scheduling order that we had negotiated and agreed upon for the parties for this particulars case was actually longer than what Your Honor had granted us. The parties had initially negotiated and proposed a longer time frame.

THE COURT: Yes. But --

MS. DADIO: And, so, in answer to your --

THE CUORT: -- why is it faster there than it is here, apart from that the Judge was firmer? Is there any other reason?

MS. DADIO: Primarily, no.

THE COURT: Why shouldn't this case then follow the schedule that is in place in Delaware?

MS. DADIO: Well, first of all, it's set up quite a bit differently as far as the way discovery has taken place. So, it would be difficult to go back at this point and rearrange --

THE COURT: What does that mean?

MS. DADIO: In that case, there is an overlap of fact discovery and expert discovery. And in this case, there is fact discovery then after that.

THE COURT: But why isn't a good deal of what's going on there similar to what's going on here, similar or almost the same. I mean, discovery review, I would assume is

the same.

MS. DADIO: Well, a large portion of the documents will be the same. And for that very reason, we'd like to have the same protective order in this case as in that case, that case having a one-tier protective order of confidentiality and to the in-house counsel.

THE COURT: You've touched on what's in the back of my mind, which is the whipsaw dimension to two cases involving essentially the same or in which the substantial substance of the case is the same.

MS. DADIO: Our proofs obviously will be different in the two cases --

THE COURT: Yes.

MS. DADIO: -- because it's two different companies. However, the defenses -- the allegations of validity and non-infringement -- obviously depend upon the particular product that are different generics. So, from the generic's perspective, they can once again almost piggyback off of each other. But from our perspective, we have to prove

separately.

THE COURT: I understand that, too. Well, in any event, I guess I understand the two issues --

MS. DADIO: If I could just --

THE COURT: -- in the protective order. I want to -- I guess apart from -- at some point, I'll stop needling you about 2008. But I guess -- unless the parties want precise coincidents in the scheduling orders and methods of dealing with these cases, it's less persuasive to me that something is not in place in Delaware that is sought here. And I'll simply ask the question are there any practical reasons why -- what

difference does it make to you if certain of their commercial information, including launch date, is only for your eyes?

MS. DADIO: Two reasons, Your Honor. Our idea is more than just convenience as far as between the two cases. Certainly, Sepracor is going to be producing hundreds of thousands of pages in this case. And, so, obviously it would be much more convenient if they could produce the same type of documents without having to re-label and re-mark different levels of confidentiality. But it's more than pure convenience. It really is a substantive issue with respect to the access that the two in-house counsel can have. Sepracor's two in-house counsel would be precluded from seeing the information that is outside counsel only. And ironically, they have actually seen -- pursuant to an offer of access of

information -- highly-confidential information of Breath. And some of that same information, Breath is now trying to say they can't see it or use it in this case. But that aside, the two in-house counsel of Sepracor are actively involved in the litigation of this matter and they need to be able -- we need to be able to rely upon them for their expertise on these matters. They're both patent attorneys. And it's -- Sepracor will be severely disadvantaged if it could not be able to rely upon their expertise in evaluating the very manufacturing process.

THE COURT: I think I understand the broad drift of it. I try to think things rather than words. And, so, to the degree that there's going to be a dispute about this, I really do want to see it in a particular context involving particular things. Like 9B practice, motion for protective order practice is not what drew me to the federal bench, so I would encourage

the parties to work hard at trying to work that aspect of it out. But I'll deal with whatever I have to deal with here.

Now, at the risk of learning, is there anything else I should be concerned about?

MS. MAZZOCHI: No, Your Honor, although we would ask that if we can't come to agreement promptly on this protective order, that we are willing to accept Sepracor's documents on an "outside attorney's eyes only" basis until a protective order is entered. So we just don't want that to be

a reason why Sepracor's document production gets held up.

THE COURT: Okay. Well, tentatively, you have acceded tentatively within committing yourself to acceding to their view on that. Then I don't see any reason why materials can't be turned over subject to refinement of the protective order in the ways that the parties want.

MS. DADIO: And in fact, the parties have previously agreed to that, Your Honor.

THE COURT: Okay. Then that seems fine. And if you file something, I'll deal with it. But you will, I'm sure, think long and hard about the filings. All right. Okay. If there's nothing further, we'll be in recess.

MS. DADIO: Thank you, Your Honor.

RECESSED AT 11:25 A.M.

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CERTIFICATION

I certify that the foregoing is a correct transcript of the record of proceedings in the above-entitled matter to the best of my skill and ability.

Pamela R. Owens Date

Official Court Reporter

EXHIBIT B

US006451289B2

(12) **United States Patent**
Wherry, III et al.

(10) **Patent No.: US 6,451,289 B2**
(45) **Date of Patent: Sep. 17, 2002**

(54) **ALBUTEROL FORMULATIONS**

(75) Inventors: **Robert J. Wherry, III**, Nashua, NH (US); **Stewart H. Mueller**, Sudbury, MA (US)

(73) Assignee: **Sepracor Inc.**, Marlborough, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/815,150**

(22) Filed: **Mar. 22, 2001**

Related U.S. Application Data

(60) Provisional application No. 60/191,910, filed on Mar. 24, 2000.

(51) **Int. Cl.**[7] **A61K 9/12**; A61K 31/135

(52) **U.S. Cl.** 424/45; 424/401; 514/653; 560/42; 206/204

(58) **Field of Search** 424/45, 401; 560/42; 206/204; 514/653

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,206,758 A		6/1980	Hallworth et al.	128/203
4,353,365 A		10/1982	Hallworth et al.	128/203
4,499,108 A		2/1985	Sequeira et al.	514/653
4,751,071 A		6/1988	Magruder et al.	424/467
4,777,049 A		10/1988	Magruder et al.	424/457
4,851,229 A		7/1989	Magruder et al.	424/457
5,362,755 A		11/1994	Barberich et al.	514/649
5,545,745 A	*	8/1996	Gao et al.	560/42
6,113,927 A	*	9/2000	Hatakeyama	424/401
6,119,853 A	*	9/2000	Garrill et al.	206/204

OTHER PUBLICATIONS

Schering, Drug Information on Proventil®, revised Aug. 1999 (obtained through on-line PDR).*

* cited by examiner

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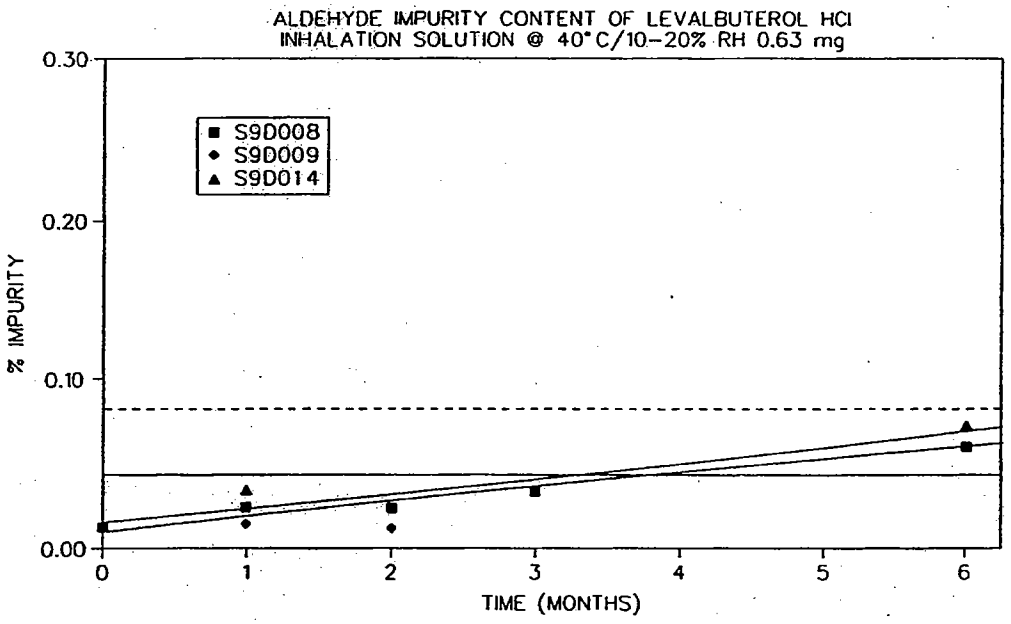
(57) **ABSTRACT**

Albuterol formulations packaged in an oxygen-permeable plastic container have a long shelf life at room temperature. The formulations consist essentially of albuterol or a pharmaceutically acceptable salt thereof, sodium chloride, and water, have a pH of about 4, and contain less than 0.08% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen.

20 Claims, 3 Drawing Sheets



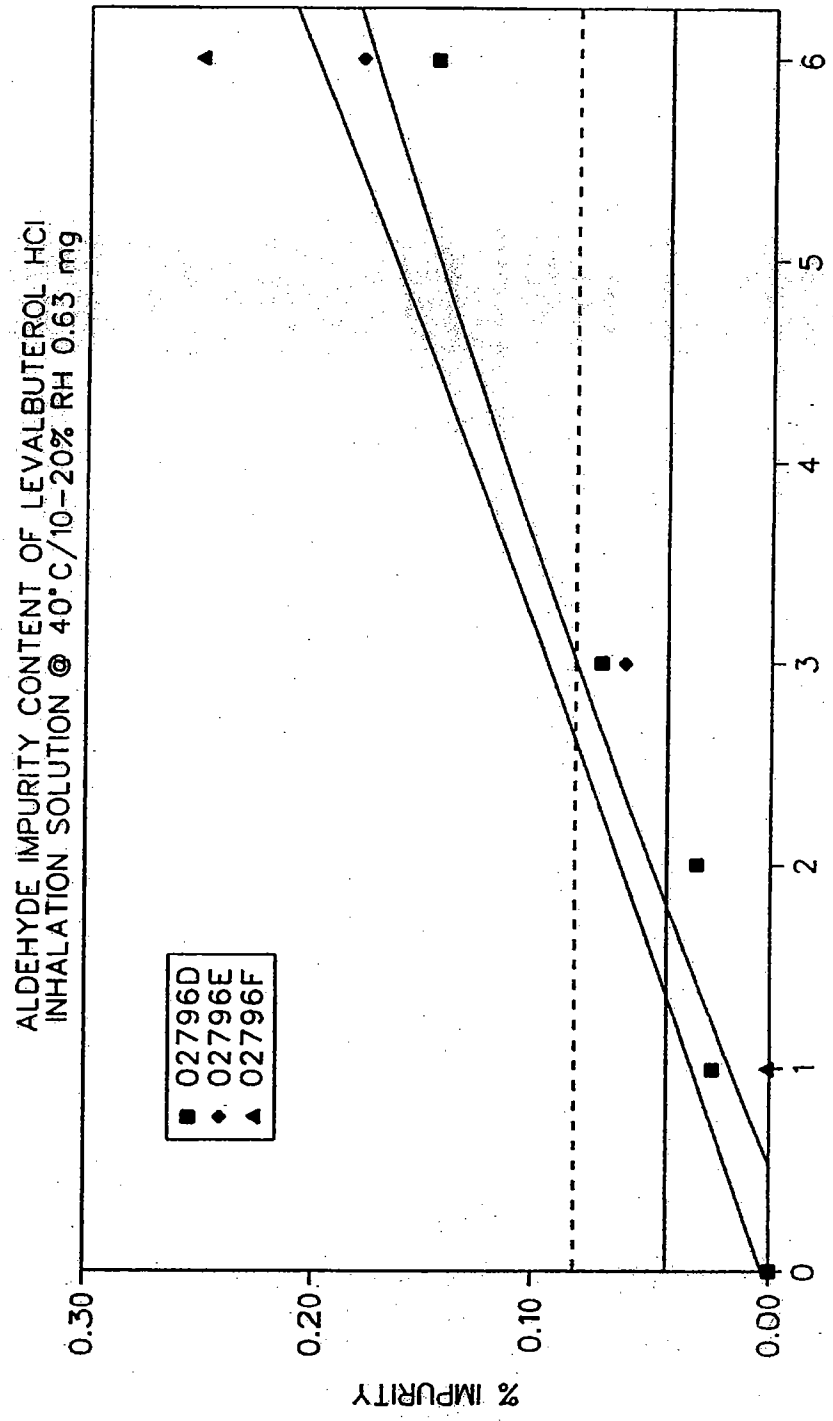

ALDEHYDE IMPURITY CONTENT OF LEVALBUTEROL HCl
INHALATION SOLUTION @ 40°C/10–20% RH 0.63 mg
02796D
02796E
02796F
% IMPURITY
0.30
0.20
0.10
0.00
TIME (MONTHS)
0
1
2
3
4
5
6

fig. 2

ALBUTEROL FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/191,910, filed Mar. 24, 2000.

FIELD OF THE INVENTION

The invention relates to packaged albuterol formulations having a long shelf life.

BACKGROUND OF THE INVENTION

An attractive method for aseptic packaging of sterile pharmaceutical solutions is an automated process called blow-fill-seal (BFS) technology, wherein plastic containers are formed, filled and sealed in one continuous operation with limited need for human intervention. An advantage of this technology is that the opportunity for microbial contamination is minimized. It has been used for the production of unit dosage vials containing albuterol.

Albuterol is an optically active compound which can exist as an (R)- or an (S)-enantiomer, or as a mixture of the two enantiomers. The term albuterol commonly refers to a racemic mixture of (R)- and (S)-albuterol. Herein, the term albuterol is defined as including a racemic mixture, a single enantiomer of albuterol, or any mixture of enantiomers of albuterol. Albuterol is a β-adrenergic antagonist and acts to relax smooth muscle. It is, therefore, particularly effective as a bronchodilator in the treatment of asthma. Racemic albuterol and racemic albuterol sulfate are commercially available as Proventil®, Ventolin® and Vormax®. The pure (R)-enantiomer, which has the generic name levalbuterol, is commercially available as Xopenex®.

It is known that albuterol degrades in aqueous solution. (See, for example, U.S. Pat. No. 4,499,108, which relates to albuterol sulfate syrups that are stable upon prolonged storage.) The cause(s) and mechanisms of the degradation reaction(s) are not well understood, but it is known that albuterol aldehyde is one of the degradation products. The level of albuterol aldehyde in an albuterol formulation for inhalation is regulated by the Food and Drug Administration because of the potentially negative effects of administering an aldehyde compound to a patient by inhalation. Currently, a maximum of 0.05% by weight albuterol aldehyde is allowed in an albuterol formulation at the time of release, with a maximum of 0.08% at the end of the expiration date. Therefore, formation of albuterol aldehyde in an aqueous albuterol solution limits the shelf life of the package containing it.

One drawback of using BFS technology for formulations of albuterol is that it has been difficult to produce a packaged formulation having a long shelf life without including additives such as chelating agents, sequestering agents, antioxidants or preservatives in the formulation or storing the package at temperatures below room temperature. It is therefore an object of the invention to provide a method of maximizing the shelf life of an albuterol formulation packaged using BFS technology.

SUMMARY OF THE INVENTION

It has been surprisingly found that when nitrogen is used as the blowing or ballooning gas in a BFS process for packaging an albuterol formulation, a package having a long shelf life is obtained. In this respect, the present invention relates to a method for manufacturing a packaged albuterol formulation having a long shelf life comprising:

blowing nitrogen gas through a hollow cylinder of an oxygen-permeable plastic and molding the hollow cylinder into an oxygen-permeable container, thereby at least partially enclosing a reduced oxygen atmosphere;

filling the oxygen-permeable container with an aqueous formulation of albuterol, or a pharmaceutically acceptable salt thereof, the aqueous formulation containing less than 0.05% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen;

enclosing the oxygen-permeable container in a reduced oxygen atmosphere within an oxygen-impermeable wrapper to produce a package enclosing an atmosphere containing less than about 2% oxygen; whereby the amount of albuterol aldehyde contained in the aqueous formulation remains lower than 0.08% by weight for a period of at least 12 months at room temperature.

In another aspect, the present invention relates to stable packaged pharmaceutical formulations consisting essentially of:

albuterol or a pharmaceutically acceptable salt thereof;

sodium chloride; and

water;

the formulation having a pH of about 4, containing less than 0.08% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen, enclosed within an oxygen-permeable plastic container, and remaining at less than 0.08% by weight of albuterol aldehyde after storage at 40° C. for six months. Preferably, the oxygen-permeable plastic container additionally encloses a gas phase comprising less than about 5% oxygen. The oxygen-permeable plastic container is preferably enclosed within a sealed wrapper comprising an oxygen-impermeable material. More preferably, the sealed wrapper additionally encloses a gas phase contained within the sealed wrapper and comprising less than about 5% oxygen.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot of % albuterol aldehyde vs. time for an albuterol formulation packaged using nitrogen as the ballooning gas.

FIG. 2 is a plot of % albuterol aldehyde vs. time for an albuterol formulation packaged without using nitrogen.

FIG. 3 is a plot of % albuterol aldehyde vs. delay time for an albuterol formulation wherein containers were filled with the formulation and wrapping of the containers was delayed. % Albuterol aldehyde was determined after storage at 40° C. for three months.

DETAILED DESCRIPTION OF THE INVENTION

According to the method of the present invention, an aqueous solution of albuterol that has a low level of dissolved oxygen is prepared for packaging. No chelating agent, sequestering agent, antioxidant, or preservative, such as edetate disodium, sodium citrate, or benzalkonium chloride, is included in the formulation. The albuterol utilized in the solution may be racemic albuterol, a single enantiomer of albuterol, or a mixture of enantiomers of albuterol. It may be in the form of the free amine or a pharmaceutically acceptable salt thereof. In a preferred embodiment, (R)-albuterol is used. (R)-Albuterol is defined as containing at least 95% by weight (R)-albuterol, preferably greater than 98% (R)-albuterol, and more preferably greater than 99% (R)-albuterol.

In another preferred embodiment, the (R)-albuterol is in the form of a pharmaceutically acceptable salt. Pharmaceu-

TABLE 1

Delayed Pouching of UDVs: % Albuterol Aldehyde After 3 Months 40 C/15% RH

Sample Type:	Replicate #:	Albuterol Aldehyde Values
Positive Control	1	0.03
	2	0.02
	3	NA
Negative Control	1	0.10
	2	0.09
	3	0.11
1 Hour	1	0.03
	2	0.03
	3	0.03
2 Hour	1	0.03
	2	0.04
	3	0.03
3 Hour	1	0.06
	2	0.03
	3	0.06
4 Hour	1	0.05
	2	0.05
	3	0.03
5 Hour	1	0.05
	2	0.03
	3	0.03
6 Hour	1	0.04
	2	0.04
	3	0.03
9 Hour	1	0.04
	2	0.03
	3	0.03
12 Hour	1	0.03
	2	0.03
	3	0.03
18 Hour	1	0.02
	2	0.03
	3	0.03
24 Hour	1	0.03
	2	0.03
	3	0.04

What is claimed is:

1. A method of manufacturing a packaged albuterol formulation having a shelf life of at least twelve months; said method comprising:

blowing nitrogen gas through a hollow cylinder of an oxygen-permeable plastic and molding the hollow cylinder into an oxygen-permeable container, thereby at least partially enclosing a reduced oxygen atmosphere;

filling the oxygen-permeable container with an aqueous formulation of albuterol, or a pharmaceutically acceptable salt thereof, said aqueous formulation being free of chelating agents, sequestering agents, antioxidants, and preservatives, and containing less than 0.05% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen;

enclosing the oxygen-permeable container under an atmosphere containing less than about 2% by weight oxygen within an oxygen-impermeable wrapper to produce a package enclosing an atmosphere containing less than about 2% by weight oxygen, and which does not contain an oxygen-absorbent.

2. A stable packaged preservative-free pharmaceutical formulation consisting essentially of:

albuterol or a pharmaceutically acceptable salt thereof;

sodium chloride; and

water;

said formulation having a pH of about 4, containing less than 0.08% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen, enclosed within an oxygen-permeable plastic container, and remaining at less than 0.08% by weight of albuterol aldehyde after storage at 40° C. for six months;

wherein said formulation does not contain a chelating agent, a sequestering agent, an antioxidant, or a preservative.

3. A stable packaged pharmaceutical formulation according to claim 2 wherein said oxygen-permeable plastic container additionally encloses a gases phase comprising less than about 5% oxygen.

4. A stable packaged pharmaceutical formulation according to claim 2 wherein said oxygen-permeable plastic container is enclosed within a sealed wrapper comprising an oxygen-impermeable material.

5. A stable packaged pharmaceutical formulation according to claim 4 wherein said sealed wrapper additionally encloses a gas phase contained within the sealed wrapper and comprising less than about 5% by weight oxygen.

6. A stable packaged pharmaceutical formulation according to claim 4 wherein a plurality of oxygen-permeable plastic containers are enclosed within said sealed wrapper.

7. A stable packaged pharmaceutical formulation according to claim 2 wherein said albuterol is (R)-albuterol.

8. A stable packaged pharmaceutical formulation according to claim 7 wherein said pharmaceutically acceptable salt is (R)-albuterol hydrochloride.

9. A stable packaged pharmaceutical formulation according to claim 2 wherein said oxygen-impermeable material is a foil laminate.

10. A stable packaged pharmaceutical formulation according to claim 2 wherein said oxygen-permeable material is low density polyethylene.

11. A preservative-free unit dosage formulation for administration by inhalation consisting essentially of:

0.18–1.4 mg albuterol or a pharmaceutically acceptable salt thereof;

27 mg sodium chloride; and

2–4 mL water;

said unit dosage formulation having a pH of about 4, containing less than 1 ppm dissolved oxygen and containing less than 0.08% by weight of albuterol aldehyde after storage at 40° C. for six months;

wherein said unit dosage formulation does not contain a chelating agent, a sequestering agent, an antioxidant, or a preservative.

12. A stable, preservative-free packaged pharmaceutical formulation, packaged according to the method of claim 1, said formulation comprising:

albuterol or a pharmaceutically acceptable salt thereof;

sodium chloride; and

having a pH of about 4, containing less than 0.08% by weight of albuterol aldehyde and less than 1 ppm dissolved oxygen, and remaining at less than 0.08% by weight of albuterol aldehyde after storage at 40° C. for six months;

wherein said formulation does not contain a chelating agent, a sequestering agent, an antioxidant, or a preservative. agent, an antioxidant, or a preservative.

13. A stable, preservative-free packaged pharmaceutical formulation according to claim 12, wherein said albuterol is (R)-albuterol.

14. A stable, preservative-free packaged pharmaceutical formulation according to claim 12 wherein said pharmaceutically acceptable salts is (R)-albuterol hydrochloride.

15. A stable, preservative-free packaged pharmaceutical formulation according to claim 12 wherein said oxygen-impermeable material is a foil laminate.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,451,289 B2
DATED : September 17, 2002
INVENTOR(S) : Wherry, III et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 6,
Line 1, delete the word "permeable"
Line 58, delete "agent, an antioxident, or a preservative."

Signed and Sealed this

Twelfth Day of August, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office